

REMARKS

Claims 34-37, 40, 45-49, 52 and 55-56 are pending and stand ready for further action on the merits. Support for new claims 55 and 56 can be found in claims 34 and 40, respectively. No new matter has been added by way of the above-amendment. This amendment does not narrow the scope of the present claims and/or has not been made for the sake of patentability.

[I] Issues Under 35 U.S.C. §112, second paragraph

Claims 34-37, 40, 45-49 and 52 are rejected under 35 U.S.C. §112, second paragraph for being indefinite. On this matter, the Examiner states:

Recitation of the term "prodrug" in claims 34-37, 40, 45-49 and 52 is deemed as indefinite. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various R, groups include such groups, namely esters, amides, alkoxycaronyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups.

Applicants respectfully submit that the present claims are not indefinite simply because the independent claims recite: 1) that the inventive compounds can be a prodrug; and 2) that the possible

variables for R^1 - R^{13} encompass moieties that have prodrug properties, i.e., they will undergo *in vivo* hydrolysis from the parent active drug.

The present claims include: A) compounds which may have one or more moiety which undergoes *in vivo* hydrolysis from the parent active drug; and B) compounds which do not have prodrug properties. Also, it is envisioned that the inventive compounds may be substituted with a single moiety that capable of splitting in more than one location by *in vivo* hydrolysis. Accordingly, simply because the present claims include compounds which can have more than one radical which undergoes *in vivo* hydrolysis to form the parent active drug, the inventive claims are not indefinite.

Applicants respectfully submit that the second paragraph of 35 U.S.C. § 112, requires that the claims particularly point out and distinctly claim the subject matter which Applicants regard as the invention. MPEP §2173.02 is instructive regarding how the Examiner should review application claims. This section states as follows:

The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available. When the examiner is satisfied that patentable subject matter is disclosed, and it is apparent to the examiner that the claims are directed to such patentable subject matter, he or she should allow claims which define the patentable subject matter with a

reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire.

Accordingly, the fact that the inventive claims include compounds which may have more than one group that can undergo in vivo hydrolysis, the inventive claims are not indefinite, and withdrawal of the rejection is respectfully requested.

[II] Issues Under 35 U.S.C. §102 and §103

The following rejections are pending:

- A. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Goulding, U.S. 5,560,864;
- B. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kam Ming Chan et al., U.S. 4,594,465;
- C. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Kurihara et al., U.S. 5,494,605;
- D. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Reiffenrath et al., U.S. 5,487,845;
- E. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Suzuki et al., U.S. 5,417,885;
- F. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gray et al., GB 2,227,742;
- G. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Raynes et al., GB 2,198,743;
- H. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Coates et al., GB 2,240,778; and
- I. Claims 34-36 and 40-49 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gray et al., GB 2,200,912.

Applicants respectfully traverse each of the rejections.

[III-A] Advantages of the Present Invention

The present invention relates to a novel para-terphenyl compound, a process for producing the same, the use of said compound as a suppressor of the IgE production for treatment as an immunosuppressor and/or an anti-allergic agent. The inventive para-terphenyl compounds have the advantage of acting as a fundamental therapeutic agent for allergic diseases, and do not merely treat the symptoms of the allergic disease. The mechanism by which this occurs is by suppression of IgE antibody production.

The art has recognized certain compounds which act to suppress IgE antibody productions such as DSCG (intal) or Nedcromil sodium. However, these compounds also affect immunoglobulins other than IgE. Because immunoglobulins are necessary for phylaxis, the inventive compounds are superior to the prior art compounds in that the inventive compounds are not only potent, but they have a high selectivity to IgE.

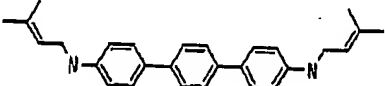
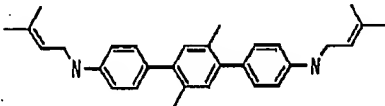
The above-explanation has been provided to highlight the patentable distinctions between the present claims and the teachings of the cited references.

[II-B] Homologue

The Examiner has not found Applicants' arguments persuasive in section [IE] beginning on page 25 of the February 1, 2002 amendment. The Examiner has maintained the position that the present claims, even though they do not contain compounds which are anticipated by the prior art, may contain compounds which are homologues of the prior art compounds. A homologue is defined as two compounds which differ by, for example, a methylene group (CH_2). In other words, the Examiner indicated that it would be obvious to modify the prior art compounds by placing a methyl group on one of the phenyl rings of the terphenyl moiety of the prior art compounds.

In response, Applicants have enclosed a Declaration Under 37 C.F.R. §1.132 by Dr. Masashi Deguchi. In the Declaration, compounds which are structurally similar to the liquid crystalline compounds taught in the cited references were prepared and tested against similar compounds containing methyl groups on the terphenyl rings. These two sets of compounds were tested for their suppressive effect on the IgE production against ovalbumin. An example of the tested compounds is provided in the following table (this data was obtained from Table 2 of the Declaration).

Table 2

| | POA | | POA |
|---|-----|--|-----|
|  | 7 |  | <0 |

These two compounds differ in the fact that the central ring of the terphenyl group has two hydrogens replaced with methyl groups. As can be seen from the data, the compound which is not substituted by the methyl groups has very little suppressive effect on the IgE production, whereas the compound containing the methyl groups on the central phenyl ring has an unexpectedly high effect on the IgE production suppressive activity.

Since each of the cited references teaches that the terphenyl derivatives have *liquid crystal properties*, the skilled artisan would not find it obvious that modifying the terphenyl rings to include methyl groups thereon, would increase their ability to *suppress IgE production*. As such, the *prima facie* case of obviousness is no longer present, and withdrawal of each of the rejections is respectfully requested.

[III] Information Disclosure Statement (IDS)

On March 1, 1999, Applicants timely filed an Information Disclosure Statement. However, the Examiner has not returned a signed copy of the enclosed PTO-1449 form. Applicants enclose a copy of this PTO-1449 form, and respectfully request that the Examiner returns a signed copy with the next communication.

[IV] International Search Report

The Examiner requests copies of the references cited in the International Search Report. In response, Applicants enclose with this amendment, copies of the requested references.

[V] Computer Search

In the third full paragraph of page 5 of the outstanding Office Action, the Examiner voices concern about the large number of prior art citations found in the Examiner's sample search.

In response, Applicants have performed an online search. A copy of the online search is enclosed for the Examiner's review. *Applicants would like to make it perfectly clear that this online search may not be comprehensive and by no means do Applicants imply that the enclosed search results should replace the Examiner's duty*

to search. The enclosed search results are merely provided to show the results of a single search strategy.

The following items 1-9 are provisos which are recited in the instant claims.

1. one or more of R^6 to R^9 are halogen, and the others of R^6 to R^9 are hydrogen
2. all of R^6 to R^9 are halogen
3. all of R^2 to R^{13} are selected from the group of hydrogen, halogen and cyano
4. all of R^6 to R^9 are hydrogen and at least one of the following is satisfied
 - 4-1 R^1 is hydrogen, fluorine, optionally substituted alkyl or optionally substituted alkoxy
 - 4-2 All of R^2 , R^3 , R^4 , R^5 and R^{12} are hydrogen
 - 4-3 R^{13} is hydrogen or halogen
5. at least one of R^6 to R^9 is other than hydrogen and at least one of the following is satisfied
 - 5-1 R^1 is methyl or acetyloxy
 - 5-2 R^{13} is hydrogen, optionally substituted alkoxy carbonyl or optionally substituted carbamoyl
 - 5-3 $-X-Y$ is methoxy
6. R^1 is acyl (The definitions of R^1 to R^{13} do not include acyl)
7. $-X-Y$ is hydroxy, hydrogen, carboxy or aryl (The definition of Y does not include hydrogen and the definition of X does not include a single bond or $-CO-$. Therefore, $-X-Y$ does not mean hydroxy, hydrogen or carboxy.)
8. at least one of R^1 to R^{13} is phenyl (The definitions of R^1 to R^{13} do not mean aryl)
9. Two or more of R^1 and R^4 , R^1 and R^2 , R^2 and R^3 ,... and R^{13} and $-X-Y$ taken together form a 5- or 6-membered ring. (Only one selected from R^1 and R^4 , R^1 and R^2 , R^2 and R^3 ,... and R^{13} and $-X-Y$ taken together may form a 5- or 6-membered ring. In the claim, " R^1 and R^4 , R^1 and R^2 ,... or R^{13} and $-X-Y$ taken together may form...")

For each terphenyl compound found in the search results, Applicants have taken the time to mark on the enclosed copy of the search results, the proviso which excludes the specific terphenyl compound. For example, on page 35 of the fax copy, a terphenyl compound is shown that has carboxy groups at the alpha and omega positions. Next to the terphenyl compound is written "3)". This means that the terphenyl compound is not encompassed by the present claims due to proviso "3" described above. The Examiner is requested to review the enclosed search results.

Conclusion

In view of the above amendments and comments, Applicants respectfully submit that the claims are in condition for allowance. A notice to such effect is earnestly solicited.

If the Examiner has any questions concerning this application, he is requested to contact the Garth M. Dahlen, Ph.D. (#43,575) at the offices of Birch, Stewart, Kolasch & Birch, LLP at the number given below.


Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of two (2) months to September 23, 2002 in which to file a reply to the Office Action. The required fee of \$400.00 is enclosed herewith.

Appl. No. 09/214,277


If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments: Copies of references
 Executed Declaration Under 37 C.F.R. 1.132
 Copies of the search results
 Copy of PTO-1449 form